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WO 02/067905 A1

(54) Title: A SUSTAINED RELEASE PHARMACEUTICAL FORMULATION

(57) Abstract: A sustained release pharmaceutical formulation is disclosed. The formulation comprises a water soluble medicament and a polymer mixture comprising a first component of about 80 weight percent polyvinylacetate combined with about 20 weight percent polyvinyl pyrrolidone, of the total weight of the first component, combined with a second component of a cellulose ether polymer.

A SUSTAINED RELEASE PHARMACEUTICAL FORMULATION

BACKGROUND OF THE INVENTION

Field of the Invention:

This invention relates to a controlled release pharmaceutical formulation, and, more particularly, to a formulation comprising (a) a water soluble medicament and (b) a mixture of polymers comprising a first mixture of polyvinyl acetate and polyvinyl pyrrolidone combined with a cellulose ether.

Description of the Related Art:

Many water soluble medicaments are poorly absorbed or transported in the body of a patient being treated, i.e. a human being or another animal, possibly due to a combination of several factors including large molecular size, ionization, high surface charge, enzymatic and chemical instability and low permeability of absorption barriers in the patient's body. In numerous therapies, drug dosimetry is increased by orders of magnitude to achieve minimum systemic concentrations required for efficiency.

The clinical and pharmaceutical chemistry sciences, in an attempt to accomplish the highest level of therapeutic benefit for those drugs or compounds, have resorted to chemical modifications as a principal mode for improving biological activity of these drugs in the body of the patient. The mode of drug administration to the body has also gradually expanded from oral and parenteral to transdermal, rectal and the pulmonary routes of administration, i.e., nose and lung. Success and achievement with these drug delivery approaches are mixed largely due to lack of acceptance of the newer, complex molecules that must be used for treating difficult diseases of the body, e.g., infections, malignancies, cardiovascular, endocrine, neurologic diseases, and a variety of immunologically compromised diseases, like AIDS.

Accordingly, what is desired and needed is a formulation system comprising an active pharmaceutical ingredient ("API") that is stable and protected by a rate-limiting carrier, easily manufactured and therapeutically effective when administered to a patient, i.e., a human being or another animal.

SUMMARY OF THE INVENTION

This invention relates to a modulated release or sustained release pharmaceutical formulation, and, more particularly, to such a formulation comprising a water soluble medicament combined with a carrier comprising a mixture of polymers.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a sustained, modulate or controlled pharmaceutical formulation comprising (1) a selected water soluble medicament or drug, (2) a suitable construct with which the drug is associated, i.e. is encapsulated therewithin or being part of the construct. The construct provides a modulated release of the associated, e.g. encapsulated, drug to the body of a patient, e.g. a human being or another animal, when the construct is administered e.g. orally, to the patient.

The formulation is ideally intended to be administered orally to the patient in a dosage form, typically, comprising a tablet.

Suitable therapeutic medicament categories of drugs or medicaments are those which are water soluble and which can be administered to a patient orally, e.g. in the form of a tablet; and include cardiovascular drugs, antiallergics, analgesics, bronchodilators, antihistamines, antitussives, antifungals, antivirals, antibiotics, other pain medicaments, antiinflammatories, etc. Particularly suitable medicaments include a pharmaceutically acceptable acid addition salt of hydroxyzine; a pharmaceutically acceptable acid addition salt of metoprolol e.g. tartrate; niacin; caffeine; theophylline; a pharmaceutically acceptable acid addition salt of diltiazem; a pharmaceutically acceptable acid addition salt of albuterol; a pharmaceutically acceptable acid addition salt of metformin; a pharmaceutically acceptable acid addition salt of metomidazole; a pharmaceutically acceptable acid addition salt of metoclopramide; a pharmaceutically acceptable acid addition salt of ranitidine; and a pharmaceutically acceptable acid addition salt of captopril.

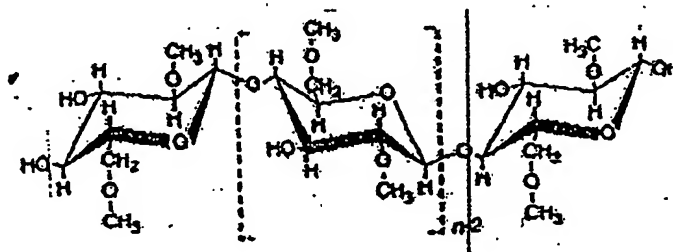
For purposes of the formulations of this invention, which are illustratively, typically intended for tableting into a tablet unit dosage form, the water soluble biotherapeutic medicament or drug is associated with the construct carrier with which it is destined to be combined. By "associate" or "associated" is meant that the

medicament is present as a matrix or a part of the matrix along with the component making up the construct or is encapsulated within the carrier matrix, or is on the surface of the carrier matrix, e.g. imbedded therein.

A suitable construct is selected. Such a construct is one which will
 5 incorporate or encapsulate the selected medicament and provide a controlled or modulated release of the medicament therefrom to the sites of action or application to the patient's body, e.g. to the hepatobiliary receptors of the human being or other animal.

A suitable carrier construct comprises a mixture of polymers. The polymer
 10 mixture comprises a first component of a first mixture, comprising about 80 weight percent polyvinyl acetate combined with about 20 weight of polyvinyl pyrrolidone; combined with a second component comprising a cellulose ether polymer. The polymer mixture comprises the first component in an amount ranging from about 30 weight percent to about 80 weight percent of the total weight of the formulation or
 15 construct and the second component ranges from about 40 weight percent to about 2 weight percent of the total weight of the formulation or construct, with the remainder comprising the water soluble medicament or mixture of medicaments, alone or with suitable excipients, as discussed hereafter.

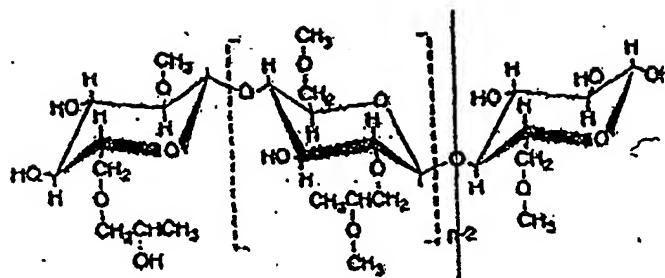
A suitable cellulose ether polymer is one having a structure
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These polymers are commercially available from the Dow Chemical Company, Midland, MI, under the Tradename "METHOCEL", e.g. METHOCEL A SERIES.
 30 Another suitable cellulosic polymer is a hydroxpropoxyl methyl cellulose polymer having a structure,

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These polymers are commercially available from the Dow Chemical Company, Midland, MI, under the tradename "METHOCEL", e.g. METHOCEL E, F, K
 10 SERIES. Preferably the formulation comprises a mixture of at least two of the foregoing components.

The dosage form, e.g. a tablet, utilizes the formulation, i.e. the construct or the matrix having the medicament associated therewith.

The water soluble medicaments of the formulation and the
 15 sustained/prolonged release unit dosage form of the present invention, e.g. a tablet, comprise a group of pharmaceutically active drugs having a solubility greater than 1 gram (g) of drug in about 200 milliliters (ml) of water.

Some drugs having such a solubility in water are metoprolol, metformin, niacin, caffeine and theophylline. Drugs not having a solubility in water greater than
 20 about 1 g/200 ml of water may be solubilized by conversion to a pharmaceutically acceptable acid or base addition salt. Preferred pharmaceutically acceptable acid addition salts include salts of mineral acids, for example, hydrochloric acid, sulfuric acid, nitric acid and the like; salts of monobasic carboxylic acids, such as, for example, acetic acid, propionic acid and the like; salts of dibasic carboxylic acids,
 25 such as, for example, maleic acid, fumaric acid, tartaric acid, succinic acid and the like; and salts of tribasic carboxylic acids, such as, for example, carboxysuccinic acid, citric acid and the like. Preferred pharmaceutically acceptable basic addition salts include salts of alkali metals, e.g. sodium or potassium; alkaline earth metals, e.g., calcium or magnesium; or complex salts, e.g., ammonium or substituted
 30 ammonium salts such as mon-, di- or trialkylammonium salts or mono, di- or trihydroxyalkylammonium salts. Some suitable drugs, in the form of their pharmaceutically acceptable salts, include hydroxyzine hydrochloride,

metoprolol tartrate, diltiazem hydrochloride, metformin hydrochloride, albuterol sulfate, metronidazole hydrochloride, metoclopramide hydrochloride, ranitidine hydrochloride, captopril dihydrochloride, brompheniramine maleate, ranitidine HCl, cimetidine HCl, ferrous sulfate, methscopolamine bromide, oxeprenolol HCl, etidronate disodium and alendronate sodium.

As previously indicated, the cellulosic polymers of the formulations and sustained/prolonged release unit dosage forms of the present invention comprise glucose polysaccharide ethers having multiple glucose units and methyl, ethyl, hydroxyethyl, hydroxypropyl or hydroxypropyl methyl substitution. Exemplary cellulosic polymers having methylether substitution are the methocels, i.e., methocel E10, methocel A4M, methocel K15M, methocel K100LV and methocel K100M, and the ethocels, for example, ethocel P20 and low-substituted hydroxypropyl ether cellulose polymers LH11, LH22 and LH30.

The formulations of the invention can be administered orally, for example, with an inert diluent. Typically the formulation is tableted using conventional grinding or granulating and tableting techniques, which include grinding or granulating the resultant formulation to a desired particle size followed by compression tableting.

For the purpose of oral therapeutic administration, the compounds can be incorporated with excipients and also used in the form of troches, capsules, chewing gums, as well as tablets. These preparations should contain at least 0.5% of active compound, but the amount can be varied depending upon the particular form and can conveniently be between 4.0% to about 70% of the weight of the unit.

Tablets, pills, capsules, troches, and the like can contain the following ingredients: a binder, such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient, such as starch or lactose; a disintergrating agent, such as alginic acid, Primogel, corn starch, and the like; a lubricant, such as magnesium stearate or Sterotex; a glidant, such as colloidal silicon dioxide; a talc; a sweetening agent, such as sucrose or saccharin; or flavoring agent, such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier, such as a fatty oil.

Other dosage unit forms can contain other materials that modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills can be coated with sugar, shellac, sustained and other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and
5 preservatives, dyes, colorings and flavors. Materials used in preparing these compositions should be pharmaceutically pure and nontoxic in the amounts used.

It is to be understood, however, that for any particular subject, specific dosage regimens should be adjusted to the individual need and the professional judgement of the person administering of the formulations of the invention. It is to
10 be further understood that any particular dosage set forth herein are exemplary only and that they do not, to any extent limit the scope or practice of the invention.

Surfactants, which may optionally be employed with the oral formulations, e.g. tablets of the present invention, comprise polysorbates, such as ethers of polyoxyethylene sorbitan and fatty acids. Exemplary surfactants are polysorbate 80
15 and polyoxyethylene 20 sorbitan monoleate, polyoxyethylene alkyl ethers of the Brig- or Volpo series, Cremophor RH, Cremophor E1, polyoxyethylene sorbitan fatty acid esters of the Tween- or Crillet series, polyoxyethylene stearates of the Cerosynt- or Myrj series, lecithin, poloxamers, d-2-tocophenyl polyethylene glycol 1000 succinate (Vitamin E TPGS) and saturated polyglycolized glycerides
20 (Labrosol, Labrafile and Gelucires), polysorbate 80 being preferred.

As indicated above, the formulations or constructs of the present invention may contain other various materials which modify the physical form of the dosage unit (the subject construct), for example, as coatings. Thus, particles of the subject controlled release formulation of the present invention may be coated with sugar,
25 shellac, sustained and other enteric coating agents. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

In a variation of the above alternative embodiment, the resultant construct is treated whereby only the top surface area thereof has a shell coating thereon. In this
30 regard, reference is made to U.S. Patent No. 5,916,584, incorporated herein by reference in its entirety, which describes the process for forming such a shell. The

resulting formulation is one which provides a delay time prior to release of the water soluble active ingredient or ingredients to the patient being treated.

It is to be understood that the water soluble medicament can be employed in the formulation alone or combined with another water soluble medicament. The amount of medicament or medicaments is one which is sufficient to therapeutically treat a disease state in the patient being treated thereby.

The term "amount" as used herein refers to a quantity or a concentration as appropriate to the context. The amount of drug that constitutes a therapeutically effective amount varies according to factors such as the potency of the particular biotherapeutic medicament the route of administration of the formulation and the mechanical system used to administer the formulation. A therapeutically effective amount of a particular drug or combination of drugs can be selected by those of ordinary skill in the art with due consideration of such factors. Generally, a therapeutically effective amount of a biotherapeutic medicament in tablet form for oral administration will be from about 1.0 mg to about 300 mg of the active ingredient or medicament.

The formulation of the water soluble medicaments of the present invention is useful for the treatment, e.g. by oral administration, of various diseases and disorders, for example, hydroxyzine hydrochloride as an anxiolytic or antihistamine, metoprolol tartrate as an antihypertensive or anti-anginal agent, niacin (nicotinic acid) as a vitamin enzyme cofactor, caffeine as a central nervous system stimulant, theophylline as a bronchodilator, diltiazem hydrochloride as an anti-anginal agent, albuterol as a bronchodilator, metronidazole as an antibacterial, methochlopramide as an anti-emetic, and captopril as an antihypertensive. The drugs are readily available from commercial suppliers.

Typically, the sustained/prolonged release pharmaceutical unit dosage forms are prepared by several process Direct compression (direct to blending of ingredients), Modified Direct Compression (partial granulation followed with direct blending), Wet Granulation (wet mass and blending of all excipients). All finished dosage forms can be followed with a combination of coating systems.

We claim:

1. A sustained/prolonged release pharmaceutical formulation comprising:
 - (a) a water soluble medicament and (b) a polymer mixture comprising a first component comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent polyvinyl pyrrolidone of the total weight of said first component, combined with a second component comprising a cellulose ether polymer.
2. A pharmaceutical unit dosage form according to claim 1 wherein said first component is present in an amount ranging from about 30 weight percent to about 80 weight percent of the total formulation and said second component ranges from about 40 weight percent to about 2 weight percent of the total weight of the formulation.
3. The formulation according to claim 2 wherein said cellulose ether is selected from the group consisting of METHOCEL A series, METHOCEL E series, METHOCEL K series, ETHOCEL P series, or a mixture of any of the foregoing ethers.
4. The formulation according to claim 3 wherein said water soluble medicament is selected from the group consisting of a pharmaceutically acceptable addition salt of hydroxyzine, a pharmaceutically acceptable addition salt of metoprolol, niacin, caffeine, theophylline, a pharmaceutically acceptable acid addition salt of diltiazem, a pharmaceutically acceptable acid addition salt of albuterol, a pharmaceutically acceptable acid addition salt of metformin, a pharmaceutically acceptable acid addition salt of metronidazole, a pharmaceutically acceptable acid addition salt of metochlopramide, a pharmaceutically acceptable acid addition salt of ranitidine and a pharmaceutically acceptable acid addition salt of captopril.
5. A pharmaceutical construct comprising:
 - (a) a water soluble medicament;
 - (b) a polymer mixture comprising (a') a first component comprising about 80 weight percent of polyvinyl acetate combined with about 20

weight percent polyvinyl pyrrolidone of the total weight of said first component; combined with (b') a second component comprising a cellulose ether polymer.

6. The pharmaceutical construct as defined in claim 5, wherein said first component is present in an amount ranging from about 30 weight percent to about 80 weight percent of the total formulation and said second component ranges from about 40 weight percent to about 2 weight percent of the total weight of the formulation

7. The pharmaceutical construct as defined in claim 6 wherein said cellulose ether is selected from the group consisting of METHOCEL A series, METHOCEL E series, METHOCEL K series, ETHOCEL P series, or a mixture of any of the foregoing cellulose ethers.

8. The pharmaceutical construct as defined in claim 7 wherein said water soluble medicament is selected from the group consisting of a pharmaceutically acceptable addition salt of hydroxyzine, a pharmaceutically acceptable addition salt of metoprolol, niacin, caffeine, theophylline, a pharmaceutically acceptable acid addition salt of diltiazem, a pharmaceutically acceptable acid addition salt of albuterol, a pharmaceutically acceptable acid addition salt of metformin, a pharmaceutically acceptable acid addition salt of metronidazole, a pharmaceutically acceptable acid addition salt of metochlopramide, a pharmaceutically acceptable acid addition salt of ranitidine, and a pharmaceutically acceptable acid addition salt of captopril.

9. A process for the preparation of a sustained/prolonged release pharmaceutical unit dosage form comprising the steps of:

- (a) fluidizing a water soluble medicament combined with a carrier, comprising a polymer mixture comprising a first component, comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent of polyvinyl pyrrolidone of the total weight of said first component, combined with a second component comprising a cellulose ether polymer; to form a fluidized mixture;
- (b) granulating said fluidized mixture to form a granulated mixture; and
- (c) tableting said granulated mixture to form a tablet.

10. The process according to claim 9 wherein said water soluble medicament is selected from the group consisting of a pharmaceutically acceptable addition salt of hydroxyzine, a pharmaceutically acceptable addition salt of metoprolol, niacin, caffeine, theophylline, a pharmaceutically acceptable acid addition salt of diltiazem, a pharmaceutically acceptable acid addition salt of albuterol, a pharmaceutically acceptable acid addition salt of metformin, a pharmaceutically acceptable acid addition salt of metronidazole, a pharmaceutically acceptable acid addition salt of metochlopramide, a pharmaceutically acceptable acid addition salt of ranitidine and a pharmaceutically acceptable acid addition salt of captopril.

11. A modulated release pharmaceutical construct which comprises a matrix of a water soluble medicament associated with a polymer mixture, where said mixture comprises a first component, comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent of polyvinyl pyrrolidone of the total weight of said first component, combined with a second component comprising a cellulose ether polymer and a medicament associated with said matrix.

12. A sustained release pharmaceutical composition comprising a construct comprising a water soluble medicament and a polymer mixture, comprising a first component comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent of the total weight of said first component of polyvinyl pyrrolidone, combined with a second component comprising a cellulose ether polymer.

13. A process for preparing a sustained/prolonged release pharmaceutical unit dosage form, which comprise:

(a) fluidizing a carrier comprising a polymer mixture comprising a first component comprising about 80 weight percent of polyvinyl acetate combined with about 20 weight percent of the total weight of said first component, combined with a second component comprising a cellulose ether polymer to form a carrier solution.

(b) adding a water soluble medicament to said carrier solution to form a medicament solution;

(c) solidifying said medicament solution to form a solid medicament construct;

- (d) granulating said medicament construct to form construct particles of a desired particle size; and
- (e) tableting said construct particles.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/01860

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/22, 9/24, 9/26, 9/28, 9/52

U.S. CL. : 424/452, 457, 465, 466, 469, 470, 472, 473, 474, 466

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/452, 457, 465, 466, 469, 470, 472, 473, 474, 466

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST: search terms: polyvinyl acetate, polyvinylpyrrolidone, cellulose ether, matrix, sustained release tablet, controlled release tablet, delayed release tablet, prolonged release tablet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,678,516 A (ALDERMAN et al) 07 July 1987, see column 2, lines 3-37.	1-13
Y	US 5,164,193 A (OKADA et al) 17 November 1992, see column 1, line 60 through column 2, line 6, column 3, lines 35-40, especially column 4, lines 44-47 and 62-66, column 5, lines 28-36, example 1, claims 1-3 and 10.	1-13
A,E	US 2002/0012701 A1 (KOLTER et al) 31 January 2002, see [0023]-[0028], [0038], [0066], example 3, claims 1-23.	1-13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T"
"A" document defining the general state of the art which is not considered to be of particular relevance	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"U" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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Date of mailing of the international search report

09 JUL 2002

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AY/2005.1829	<div style="display: flex; justify-content: space-between;"> <div> FOR FURTHER ACTION </div> <div> see Form PCT/ISA/220 as well as, where applicable, item 5 below. </div> </div>	
International application No. PCT/SG2005/000102	International filing date (<i>day/month/year</i>) 29 March 2005	(Earliest) Priority Date (<i>day/month/year</i>) 30 March 2004
Applicant AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of **4** sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II).

3. ☐ Unity of invention is lacking (See Box No. III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. **1**

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

- b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SG2005/000102

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 7: A61K 31/522, 9/22, 47/38, 47/34; A61P 25/28, 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 Medline, DWPI keywords: caffeine, xanthine, +phylline+, theobromine, sustained, constant, control+, hydrophylic(polymer, +cellulose+, PVP, Polyvinylpyrrolidone, Poly(ethylene)oxide

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/067905A (KOS Pharmaceuticals, Inc.) 6 September 2002. See pages 3, 4, 5 and 7.	1-4, 20-22, 28
X	Derwent Abstract Accession No. 91-291715/40, Classes A96, B07, B04, JP 03-193734 A (Eisai KK) 23 August 1991	1-4, 20-22, 28
X	Durig T, Fassihi R. "Mechanistic evaluation of binary effects of magnesium stearate and talc as dissolution retardants at 85% drug loading in an experimental extended-release formulation." J Pharm Sci. 1997 Oct; 86(10):1092-8. See page 1093 especially.	20-22, 28
X	Saha RN, Sajeew C, Sahoo J. "A comparative study of controlled release matrix tablets of diclofenac sodium, ciprofloxacin hydrochloride, and theophylline." Drug Deliv. 2001 Jul-Aug; 8(3): 149-54. See page 149, Table 1 and Fig. 3	20-22, 28



Further documents are listed in the continuation of Box C



See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

1 June 2005

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Name and mailing address of the ISA/AU

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2005/000102

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Leslie S., "The Contin delivery system: dosing considerations." J Allergy Clin Immunol. 1986 Oct; 78 (4 Pt 2): 768-73. See page 768 and Fig. 2	20-22, 28
X	Prabakaran D, et al, "Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and in vitro characterization." Int J Pharm. 2004 Oct 13; 284(1-2): 95-108. See Abstract, Tables 1-4	20-34

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/SG2005/000102

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.			
END OF ANNEX			